

## Effect of atenolol and metoprolol on the anticoagulant activity of acenocoumarin

F. MANTERO, M. PROCIDANO, M. A. VICARIOTTO & A. GIROLAMI

Institute of Medical Semeiotics, Medical School, University of Padua, Via Ospedale 105, 35100 Padova, Italy

In patients receiving long-term acenocoumarin treatment, the effect on anticoagulant activity of atenolol (100 mg once-daily) and metoprolol (100 mg twice daily) was compared in a randomised within-patient open trial. No significant differences were demonstrated between mean prothrombin time and Thrombotest during treatment with atenolol, metoprolol or placebo. These data do not suggest the existence of an interaction between acenocoumarin and the moderately lipophilic  $\beta$ -adrenoceptor blocker metoprolol, or the hydrophilic  $\beta$ -adrenoceptor blocker atenolol. The results are discussed in the light of published data for the highly lipophilic  $\beta$ -adrenoceptor blocker propranolol.

**Keywords** acenocoumarin anticoagulants atenolol metoprolol pharmacokinetics

### Introduction

$\beta$ -adrenoceptor blockers lower the clearance of some drugs which are metabolised by the liver (such as lignocaine and antipyrine), probably by a direct inhibition of drug-metabolising microsomal enzymes. This effect has been directly correlated with the  $\beta$ -adrenoceptor blockers' lipid solubility as expressed by octanol/buffer pH 7.4 partition coefficient, propranolol being the most lipophilic (Deacon *et al.*, 1981). Since many drugs are metabolised by similar hepatic microsomal mechanisms, it is suggested that an interaction between these substances and lipophilic  $\beta$ -adrenoceptor blockers may exist, as has been demonstrated for cimetidine (Houtzagers *et al.*, 1982). However, this phenomenon may be clinically relevant only for drugs with low therapeutic indices, such as the oral anticoagulants. A case has recently been described in which propranolol may have enhanced the anticoagulant effect of warfarin (Bax *et al.*, 1983).

The present study was designed to verify whether the anticoagulant effect of acenocoumarin (which is very similar to warfarin) is potentiated by the concomitant administration of  $\beta$ -adrenoceptor blockers. Furthermore, the relationship between increasing lipid-solubility

of two  $\beta$ -adrenoceptor blockers (atenolol and metoprolol) and their degree of interaction was investigated.

### Methods

Nine males and females (aged 20-65 years) on long-term treatment with acenocoumarin (one with warfarin), for recurrent episodes of thrombophlebitis, were included in the study. The patients were chosen from those who presented constant values for prothrombin time during the 3 months before entering the study on an out-patient basis. Exclusion criteria included medical conditions which contra-indicated the use of  $\beta$ -adrenoceptor blockers, clinically important valvular heart disease, and liver, kidney or thyroid disorders.

During long-term acenocoumarin treatment, a randomised within-patient open comparison of atenolol (100 mg once daily), metoprolol (100 mg twice daily) and placebo was performed, each treatment being for a 3-week period. Prothrombin time, Thrombotest, blood pressure

and heart rate were measured weekly, and liver function tests were performed before and after each 3-week treatment period.

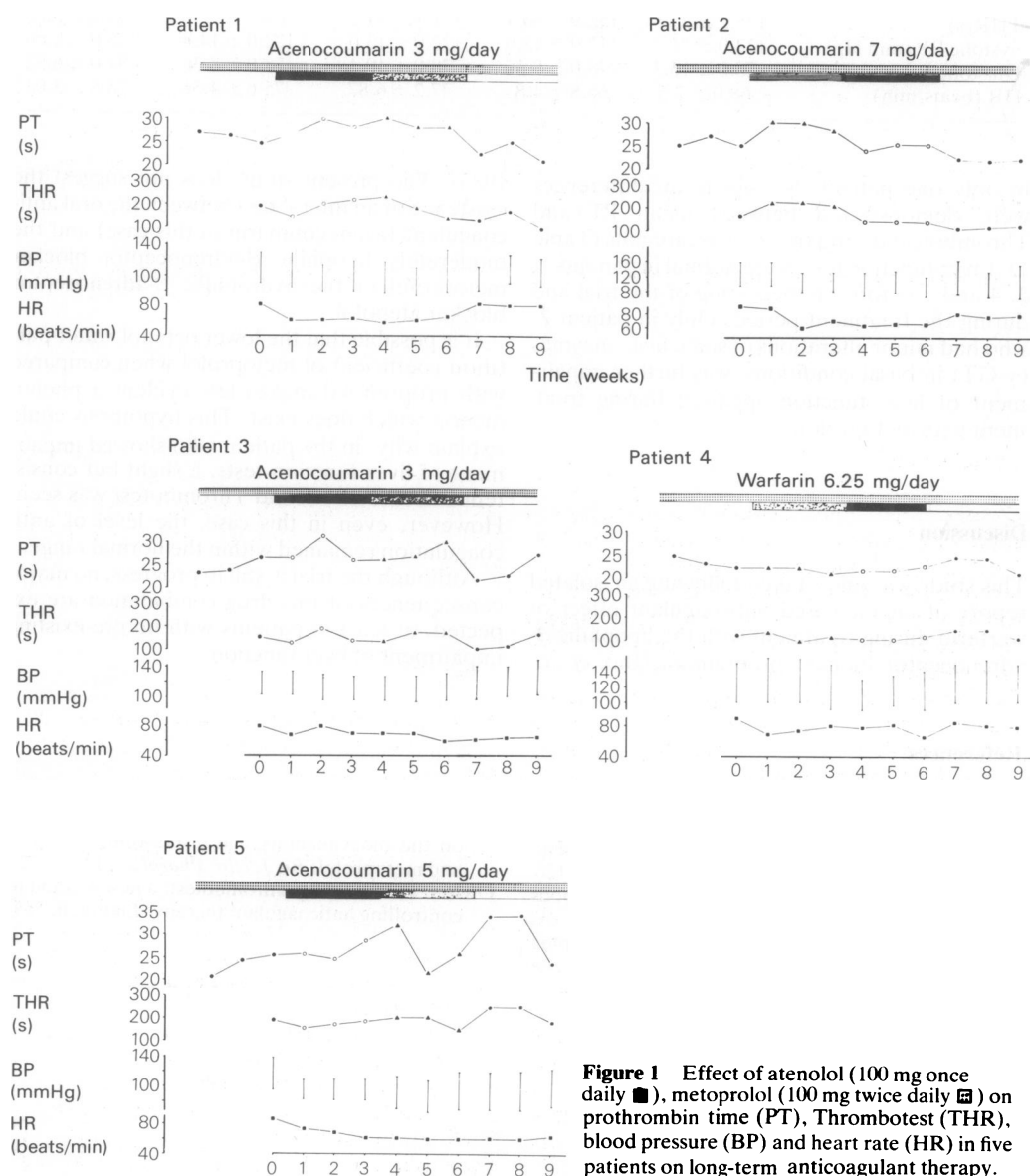
Prothrombin time (PT) was measured by standard procedures using a rabbit brain and lung thromboplastin (Simplastin, General Diagnosis, Morris Plains, N.J., U.S.A.) Thrombotest (Nyegaard, Oslo, Norway) was performed on citrated plasma using the method proposed by Owren (1959).

Since the trial is still in progress, only results obtained from the first five patients are presented.

## Results

The effects of atenolol, metoprolol and placebo on PT, THR, BP and HR in five patients are shown in Figure 1. Only in one patient (the single patient treated with warfarin) was there stability in the levels of anticoagulation, without change during the trial period. Slight and temporary extensions of PT and Thrombotest were observed during atenolol and metoprolol treatment in patients 1, 3 and 5.

PT and Thrombotest values were slightly but consistently higher during metoprolol treatment



**Figure 1** Effect of atenolol (100 mg once daily ■), metoprolol (100 mg twice daily □) on prothrombin time (PT), Thrombotest (THR), blood pressure (BP) and heart rate (HR) in five patients on long-term anticoagulant therapy.

**Table 1** Mean values ( $\pm$  s.d.) of prothrombin time (PT), Thrombotest (THR), blood pressure (BP) and heart rate (HR) in five patients in long-term oral anticoagulant treatment during atenolol (A), metoprolol (M) and placebo (P). Numbers (1, 2, 3) indicate week of treatment.

Variable	Basal values	A1	A2	A3	M1
PT(s)	25.26 $\pm$ 2.17	25.2 $\pm$ 2.03	28.32 $\pm$ 2.9	26.42 $\pm$ 2.26	28.48 $\pm$ 3.9
THR(s)	162.24 $\pm$ 29.8	141.3 $\pm$ 20.1	166.1 $\pm$ 34.2	147.14 $\pm$ 40.3	187.5 $\pm$ 45.4
Systolic BP (mm Hg)	137.0 $\pm$ 6.7	119.0 $\pm$ 7.41	117.0 $\pm$ 7.6	116.0 $\pm$ 8.9	130.0 $\pm$ 2.2
Diastolic BP (mm Hg)	88.0 $\pm$ 13.5	72.0 $\pm$ 10.36	76.0 $\pm$ 8.21	72.0 $\pm$ 8.36	79.0 $\pm$ 14.7
HR (beats/min)	91.2 $\pm$ 5.21	70.8 $\pm$ 9.9	76.0 $\pm$ 13.56	65.6 $\pm$ 6.06	72.8 $\pm$ 11.7

Variable	M2	M3	P1	P2	P3
PT(s)	25.48 $\pm$ 3.7	26.72 $\pm$ 3.26	25.38 $\pm$ 5.4	26.08 $\pm$ 5.13	23.1 $\pm$ 2.68
THR(s)	175.2 $\pm$ 27.8	152.9 $\pm$ 30.4	151.3 $\pm$ 54.2	165.0 $\pm$ 52.6	139.3 $\pm$ 32.8
Systolic BP (mm Hg)	122.0 $\pm$ 21.7	117.0 $\pm$ 13.0	122.0 $\pm$ 13.0	122.0 $\pm$ 14.4	125.0 $\pm$ 8.66
Diastolic BP (mm Hg)	76.0 $\pm$ 16.3	73.0 $\pm$ 8.36	78.0 $\pm$ 10.4	78.0 $\pm$ 8.36	81.0 $\pm$ 6.52
HR (beats/min)	68.0 $\pm$ 7.5	66.8 $\pm$ 4.8	77.2 $\pm$ 6.87	75.6 $\pm$ 4.56	76.8 $\pm$ 3.03

in only one patient. No significant differences were demonstrated between mean PT and Thrombotest during the three treatments (Table 1). Liver function tests were normal in patients 1, 3, 4 and 5 before the beginning of the trial and during the treatment period. Only in patient 2, who had minor alterations of some liver enzymes ( $\gamma$ -GT) in basal conditions, was further impairment of liver function apparent during treatment with metoprolol.

## Discussion

This study was undertaken following an isolated report of an increased anticoagulant effect of warfarin during treatment with the lipophilic  $\beta$ -adrenoceptor blocker propranolol (Bax *et al.*,

1983). The present study does not suggest the existence of an interaction between the oral anti-coagulant (acenocoumarin in this case) and the moderately lipophilic  $\beta$ -adrenoceptor blocker metoprolol or the hydrophilic  $\beta$ -adrenoceptor blocker atenolol.

It is possible that the lower octanol/water partition coefficient of metoprolol when compared with propranolol makes less evident a phenomenon which does exist. This hypothesis could explain why, in the patient who showed impairment of liver function tests, a slight but consistent increase of PT and Thrombotest was seen. However, even in this case, the level of anticoagulation remained within the normal range.

Although the trial is still in progress, no major consequences of this drug combination are expected, at least in patients with no pre-existing impairment of liver function.

## References

- Bax, N. D. S., Lennard, M. S., Al-Asady, S., Deacon, C. S., Tucker, G. T. & Woods, H. F. (1983). Inhibition of drug metabolism by beta-adrenoceptor antagonists. *Drugs*, **25** (Suppl. 2), 121–126.
- Deacon, C. S., Lennard, M. S., Bax, N. D. S., Woods, H. F. & Tucker, G. T. (1981). Inhibition of oxidative drug metabolism by  $\beta$ -adrenoceptor antagonist is related to their lipid solubility. *Br. J. clin. Pharmacol.*, **12**, 429–431.
- Houtzagers, J. J. R., Streurman, O. & Regardh, C. G. (1982). The effect of pretreatment with cimetidine on the bioavailability and disposition of atenolol and metoprolol. *Br. J. clin. Pharmacol.*, **14**, 67–72.
- Owren, P. A. (1959). Thrombotest: a new method for controlling anticoagulant therapy. *Lancet*, **ii**, 754.